Phase II Trial of Vinflunine in Relapsed Small Cell Lung Cancer

David R. Spigel, MD,† John D. Hainsworth, MD,*† Cassie M. Lane, MS,* Bobby Clark, PhD,* Howard A. Burris, III, MD,*† and F. Anthony Greco, MD*†*

Background: Vinflunine is a new microtubule inhibitor with preclinical activity in small cell lung cancer (SCLC). In this phase II trial, we evaluated vinflunine in patients with relapse-sensitive and refractory SCLC.

Methods: This trial aimed to achieve a 20% objective response rate (ORR) in platinum-sensitive patients. Patients with Eastern Cooperative Oncology Group performance status 0 to 2 and measurable disease received vinflunine (320 mg/m^2 IV) every 21 days (≤6 cycles; response evaluation every 6 weeks).

Results: Patient characteristics (N = 51): median age 63 years (range, 37–85 years); male, 55%; Eastern Cooperative Oncology Group performance status 2, 16%; relapse-sensitive SCLC, 53%. The overall ORR was 19.6% (95% confidence interval [CI] 10–33%). Twelve (23.5%) patients had stable disease; 18 (35.3%) patients had progressive disease. Among relapse-sensitive patients, ORR was 22.2% (95% CI 9–42%). Among relapse-refractory patients, ORR was 16.7% (95% CI 5–37%). Median follow-up was 15 months (range, 12–18 months); median progression-free survival (PFS) was 1.6 months (95% CI 1.3–3.9 months); median overall survival (OS) was 4.9 months (95% CI 3.2–6.5 months). Among relapse-sensitive patients, PFS and OS were 1.6 and 4.9 months, respectively. Among relapsed-refractory patients, PFS and OS were 1.4 and 4.0 months, respectively. In general, vinflunine was well tolerated, although neutropenia was a notable toxicity. Grade 3/4 toxicities (>5%): neutropenia (32%), arthralgia/myalgia (16%), fatigue (16%), hyponatremia (12%), leukopenia (12%), nausea/vomiting (12%), constipation (6%), and thrombocytopenia (6%). The rates of toxicities were relatively well balanced among relapse-sensitive and refractory patients; one patient died of sepsis that was possibly treatment related.

Conclusions: Vinflunine has activity in relapsed SCLC, including refractory relapsed patients. Neutropenia was common but associated with rare febrile episodes. Additional study in relapse-refractory SCLC is indicated.

*Sarah Cannon Research Institute, and †Tennessee Oncology, PLLC, Nashville, Tennessee.

Disclosure: All coauthors state that they have no relevant financial interests in this manuscript.

Address for correspondence: David R. Spigel, MD, Sarah Cannon Research Institute, 250 25th Avenue North, Suite 110, Nashville, TN 37203. E-mail: dspigel@tnonc.com

Preliminary data presented at the American Society of Clinical Oncology Annual Meetings, Orlando, FL, 2007, and Chicago, IL, 2008.

ISSN: 1556-0864/10/0506-0874

Key Words: Vinflunine, Relapse, Single-agent therapy, Small-cell lung cancer.

(*J Thorac Oncol.* 2010;5: 874–878)

Majority of patients diagnosed with small cell lung cancer (SCLC) will relapse and die of disease despite achieving high response rates with combination first-line therapy.[1] The only Food and Drug Administration-approved therapy for patients with relapse-sensitive SCLC (disease that responded to first-line therapy but subsequently progressed at least 60–90 days after treatment) is topotecan. This approval was based on improved symptoms seen in a randomized trial comparing topotecan with cyclophosphamide, doxorubicin, and vincristine in patients with relapse-sensitive SCLC.[2] An oral formulation was recently approved based on equivalence to the intravenous formulation and benefit over supportive care alone.[3,4] Despite these approvals, topotecan is associated with a modest response rate (range, 7–24%) and survival (5.8–8.8 months). There are no approved therapies for patients with relapse-refractory SCLC (disease that progresses within 60–90 days of first-line therapy). Newer therapies are needed.

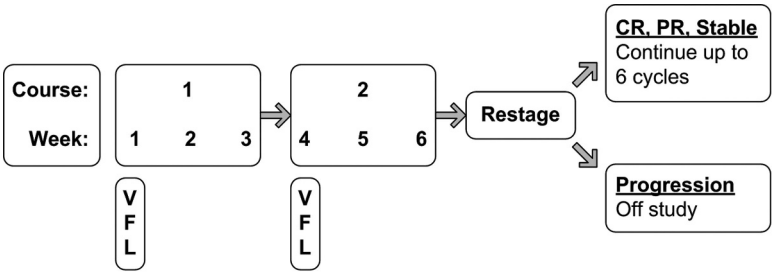
Vinflunine is a new vinca alkaloid microtubule inhibitor that causes cell cycle arrest and apoptosis.[5,6] Vinflunine demonstrated pronounced activity in multiple cancer cell lines, including small cell lung cancer.[7–10] This early efficacy prompted clinical investigation of single agent vinflunine in multiple solid tumor settings, including non-small cell lung cancer and mesothelioma.[11–16] Herein, we report on a multicenter phase II trial where vinflunine was administered to patients with relapse-sensitive and refractory SCLC.

PATIENTS AND METHODS

This trial was initiated in March 2006. Participating centers included the Sarah Cannon Research Institute and selected sites from the Sarah Cannon Oncology Research Consortium, a national community-based research network.

Patients

Patients with SCLC who had progressed after one previous chemotherapy or chemotherapy/radiation regimen were enrolled. Patients who had progressive tumor or relapse more than 3 months since the end of the last cycle of chemotherapy were considered "relapse-sensitive" patients. Patients who had progressive tumor or relapse within 3



VFL: Vinflunine 320 mg/m^2 IV every 21 days

Courses repeated at 21-day intervals. Restaging every 2 cycles.

FIGURE 1. Treatment plan.

months of chemotherapy ending were considered "relapse-refractory" patients. Patients had measurable disease per Response Evaluation Criteria in Solid Tumors (RECIST).[17] Other eligibility criteria included age ≥18 years; presence of untreated brain metastases, Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0 to 2; and adequate organ function (defined as absolute neutrophil count [ANC] $\geq 1.0 \times 10^9$/L, platelet count $\geq 100 \times 10^9$/L, serum bilirubin $\leq 1.25 \times$ the upper limit of normal serum aspartate transaminase $< 5 \times$ the upper limit of normal, and serum creatinine ≤2.0 mg/dL).

Exclusion criteria included pregnancy or lactation; clinically significant cardiovascular disease; or other active malignancy. All patients provided written informed consent before enrollment.

Pretreatment Evaluation

Before treatment, patients were evaluated by history, physical examination, and laboratory testing. Baseline tumor staging was performed using computed tomography (CT) of the chest, abdomen, and pelvis; CT or magnetic resonance imaging of the brain; and bone scan or positron emission tomography.

Treatment Plan

All patients received vinflunine 320 mg/m^2 every 21 days as a 15- to 20-minute infusion (reconstituted in 100 mL of 0.9% normal saline) (Figure 1). Additional support included hydration, fiber supplements, and laxatives. Patients were restaged with CT scans every 2 cycles or 6 weeks (per RECIST). If there was no evidence of disease progression or significant toxicity, patients received up to 6 cycles.

Dose modifications were based on ANC and platelet counts on day 1 of each cycle; and doses were not increased once modified. No adjustments were required if the ANC was $\geq 1.0 \times 10^9$/L and platelet count $\geq 100 \times 10^9$/L. If the ANC was $< 1.0 \times 10^9$/L or platelets $< 100 \times 10^9$/L, chemotherapy was held until counts recovered to baseline parameters. Patients requiring hospitalization for neutropenia and fever had dose reductions (first episode: 280 mg/m^2, second episode: 250 mg/m^2). Chemotherapy was also reduced for severe nonhematologic toxicity.

Toxicity assessments were made according to the common terminology criteria for adverse events (version 3.0) of the National Cancer Institute. Cytokines were not administered with the first course of treatment; however, prophylactic granulocyte colony-stimulating factor for patients experiencing febrile neutropenia was permitted at the discretion of the treating physician and was not to substitute for mandated dose reductions.

This trial was approved by the institutional review boards of all participating institutions and was conducted in accordance with Food and Drug Administration Good Clinical Practices and local, ethical, and legal requirements. The Sarah Cannon Research Institute designed and coordinated the trial and was responsible for all aspects of data collection and analysis. Vinflunine was provided by Bristol-Myers Squibb (New York, NY).

TABLE 1. Patient Characteristics ($n = 51$)

Characteristic	No. of Patients (%)
Median age, yr (range)	63 (37–85)
Sex	
Male	28 (55)
Female	23 (45)
ECOG PS	
0	13 (25)
1	30 (59)
2	8 (16)
Relapse category	
Refractory	24 (47)
Sensitive	27 (53)
Metastatic sites	
Bone	18 (35)
Liver	26 (51)
Lymph nodes	27 (53)
Pleural effusion	6 (12)
Central nervous system	4 (8)
Other	15 (29)
Site of treatment	
Tennessee oncology	14 (27)
Network sites	37 (73)

ECOG, Eastern Cooperative Oncology Group; PS, performance status.

TABLE 2. Response Rates

Best Response	Total (n = 51) No. of Patients (%)	Refractory (n = 24) No. of Patients (%)	Sensitive (n = 27) No. of Patients (%)
CR	0	0	0
PR	10 (19.6)	4 (16.7)	6 (22.2)
SD	12 (23.5)	6 (25)	6 (22.2)
PD	18 (35.3)	9 (37.5)	9 (33.3)
UE	11 (21.6)	5 (20.8)	6 (22.2)

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; UE, unevaluable.

Definition of Response

All patients were evaluated for response by RECIST criteria. The final response category assigned represented the best response obtained during treatment.

Statistical Methods

The primary objective of this phase II trial was to assess the overall objective response rate (ORR) in patients with relapsed SCLC treated with single agent vinflunine. If the administration of intravenous vinflunine failed to provide efficacy that was at least comparable with the average experience of single agent topotecan (i.e., 20%) in relapse-sensi-

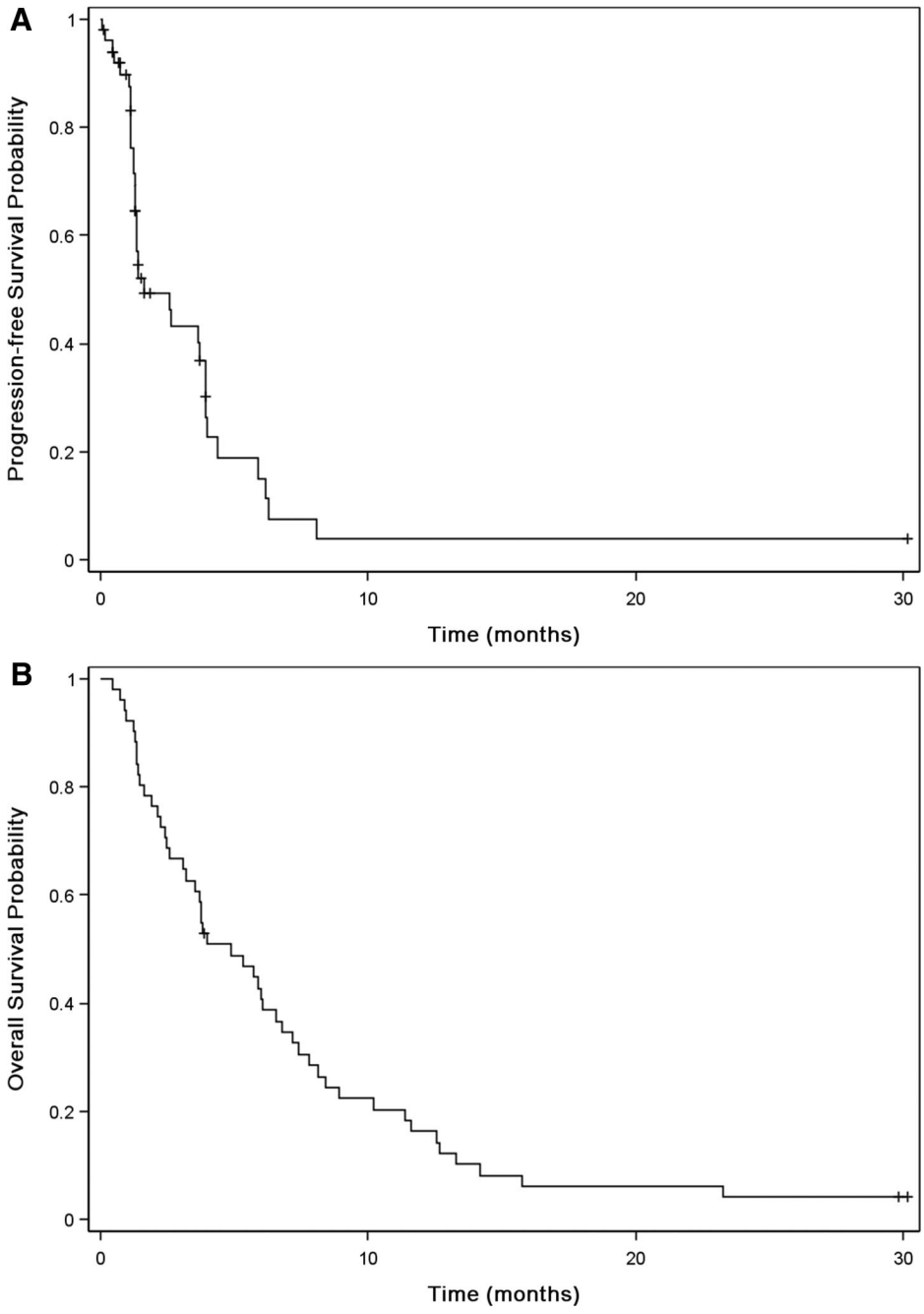


FIGURE 2. Progression-free survival and overall survival.

tive SCLC, then there would not be further interest in developing the proposed regimen in this population. Secondary end points included assessments of toxicity, progression-free survival (PFS), overall survival (OS), and duration of response.

It was hypothesized that vinflunine would result in an objective response of ≥20% in the intent-to-treat population. This trial employed a Simon optimal design. For a total of 41 subjects, 21 would be accrued during stage 1, and 20 during stage 2. The alpha level of the design was 0.05; and the power was 0.9.

Efficacy outcomes were based on intent-to-treat analyses. PFS was defined as the interval between the start date of treatment and the date of occurrence of progressive disease or death. OS was measured from the date of study entry until the date of death. Survival curves were constructed using the method of Kaplan and Meier.[18]

RESULTS

Patient Characteristics

Fifty-one patients were enrolled from March 2006 to April 2007, 27% from our Nashville, TN, site and 67% from other consortium sites. Baseline characteristics for all patients are described in Table 1. The median age was 63 years (range, 37–85 years). Twenty-eight (55%) patients were men and 23 patients were women. ECOG PS was 0 in 13 (25%) patients, 1 in 30 (59%) patients, and 2 in 8 (16%) patients. Twenty-four (47%) patients had relapse-refractory SCLC and 27 patients had sensitive disease. Metastatic sites included liver (51%), lymph nodes (53%), and bone (35%), among other sites.

Treatment Received

The median follow-up is 15 months (range, 12–18 months). Eleven (22%) patients were not evaluable for a response because of treatment compliance (1 patient), clinical progression without documented imaging (3 patients), poor clinical response/worsening symptoms (1 patient), physician discretion (1 patient) death due to disease (3 patients), and treatment-related toxicity (pain and constipation in 1 patient and sepsis and hematologic toxicity in 1 patient). All these patients were included in the efficacy analyses.

Response

The overall ORR was 19.6% (10 of 51 patients) (95% confidence interval [CI] 10–33%) (Table 2). There were no complete responses. Twelve (23.5%) patients had stable disease and 18 (35.3%) patients had progressive disease. The median response duration was 2.7 months (95% CI 1.9–3.9%). Among relapse-sensitive patients, the ORR was 22.2% (95% CI 9–42%). Among relapse-refractory patients, the ORR was 16.7% (95% CI 5–37%).

Progression-Free Survival and Survival

The median PFS was 1.6 months (95% CI 1.3–3.9 months) (Figure 2*A*). The median OS was 4.9 months (95% CI 3.2–6.5 months) (Figure 2*B*). One-year OS was 16% (95% CI 8–28%). Among relapse-sensitive patients, PFS, median OS, and 1-year OS were 1.6 months, 4.9 months, and 7%, respectively. Among relapse-refractory patients PFS, median OS, and 1-year OS were 1.4 months, 4.0 months, and 27%, respectively.

Treatment-Related Toxicity

Treatment-related toxicity is summarized in Table 3. In general, vinflunine was well tolerated although neutropenia was a notable toxicity. Neutropenic fever occurred in 1 (2%) patient overall. The most common (>3%) grade 3/4 toxicities were neutropenia (32%), leukopenia (12%), thrombocytopenia (6%), anemia (4%), fatigue (16%), nausea/vomiting (12%), arthralgia/myalgia (16%), dyspnea (4%), hyponatre-

TABLE 3. Grade 3/4 Treatment-Related Toxicity in ≥4% of Patients (n = 51; 149 Treatment Cycles)

	No. of Patients (%)					
	Refractory Relapse (n = 24)		Sensitive Relapse (n = 27)		Total (n = 51)	
Toxicity	G3	G4	G3	G4	G3	G4
Hematologic						
Hemoglobin	0	1 (4)	1 (4)	0	1 (2)	1 (2)
Leukocytes	2 (8)	1 (4)	2 (7)	1 (4)	4 (8)	2 (4)
Neutrophils	3 (13)	5 (21)	3 (11)	5 (19)	6 (12)	10 (20)
Platelets	2 (8)	1 (4)	2 (7)	0	2 (4)	1 (2)
Neutropenic fever	0	0	1 (4)	0	1 (2)	0
Nonhematologic						
Fatigue	4 (17)	0	4 (15)	0	8 (16)	0
Nausea/vomiting	4 (17)	0	2 (7)	0	6 (12)	0
Arthralgia/myalgia	4 (17)	0	4 (15)	0	8 (16)	0
Dyspnea	2 (8)	0	0	0	2 (4)	0
Hyponatremia	2 (8)	0	1 (4)	3 (11)	3 (6)	3 (6)
Constipation	2 (8)	0	1 (4)	0	2 (6)	0
Anorexia	1 (4)	0	1 (4)	0	2 (4)	0

mia (12%), constipation (6%), and anorexia (4%). The rates of toxicities were relatively well balanced among relapse-sensitive and refractory patients. Fifty-three percent of patients experienced grade 1 or 2 constipation. One patient died of sepsis that was possibly treatment related.

DISCUSSION

Fifty percent of patients diagnosed with SCLC will relapse within 4 to 6 months of first-line therapy. There are limited treatment options for these patients, half of whom will not survive the first year.[1,3,19] Topotecan is commonly used in the relapsed setting but is associated with severe neutropenia and modest efficacy.[2] Newer therapies are needed for these patients.

Vinflunine is a novel microtubule inhibitor that has demonstrated antitumor activity in multiple cell lines, including SCLC. Preliminary clinical activity has been observed in patients with breast, genitourinary, and lung cancers.[11–16,20] The 21-day dosing is relatively more convenient than 5-day dosing with topotecan and is well tolerated and safe.

In this phase II study, vinflunine resulted in partial responses in 20% of patients with relapsed SCLC. This rate is equivalent to rates observed with topotecan in prospective clinical trials.[2–4] Notably, vinflunine also achieved partial responses in 17% of patients with relapse-refractory SCLC, a rate that is substantially higher than expected in this patient subset. Unfortunately, the overall response rate did not translate into an extended survival in the overall population. In general, the toxicity was expected and relatively modest overall, although severe neutropenia was observed in one-third of patients and may have contributed to one patient death due to sepsis.

This trial is limited by its single cohort design and small subsets of relapsed patients. The confidence interval is wide for the response rate in the refractory subset and may be substantially different in a larger prospective trial. In addition, most of the patients enrolled in this trial had an ECOG PS of 0 or 1, despite allowing for a PS of 2. This may not best reflect what many of the sicker patients' oncologists encounter in the relapsed setting and potentially overestimates the treatment benefit for other patients.

In summary, vinflunine is a new vinca alkaloid that seems to be well tolerated as a single agent in patients with relapsed SCLC. In this multicenter community-based trial, vinflunine seemed to have activity in both relapse-sensitive and refractory patients, with acceptable toxicity. Additional study in relapse-refractory SCLC is warranted. Ongoing trials in other tumor settings with vinflunine may help to further characterize its overall safety and potential future role in clinical care.

ACKNOWLEDGMENTS

Supported in part by a grant from Bristol-Myers Squibb, New York, NY.

REFERENCES

1. Schiller JH, Adak S, Cella D, et al. Topotecan versus observation after cisplatin plus etoposide in extensive-stage small-cell lung cancer: E7593—a phase III trial of the Eastern Cooperative Oncology Group. *J Clin Oncol* 2001;19:2114–2122.
2. von Pawel J, Schiller JH, Shepherd FA, et al. Topotecan versus cyclophosphamide, doxorubicin, and vincristine for the treatment of recurrent small-cell lung cancer. *J Clin Oncol* 1999;17:658–667.
3. Eckardt JR, von Pawel J, Pujol JL, et al. Phase III study of oral compared with intravenous topotecan as second-line therapy in small-cell lung cancer. *J Clin Oncol* 2007;25:2086–2092.
4. O'Brien MER, Ciuleanu TE, Tsekov H, et al. Phase III trial comparing supportive care alone with supportive care with oral topotecan in patients with relapsed small-cell lung cancer. *J Clin Oncol* 2006;24:5441–5447.
5. Etievant C, Barret JM, Kruczynski A, et al. Vinflunine (20′,20′-difluoro-3′,4′-dihydrovinorelbine), a novel vinca alkaloid, which participates in P-glycoprotein (Pgp)-mediated multidrug resistance *in vivo* and *in vitro*. *Invest New Drugs* 1998;16:3–17.
6. Jacquesy JC, Fahy I. Cancer: superacidic generation of new antitumour agents. In PF Torrens, (Ed.), Biomedical Chemistry: Applying Chemical Principals to the Understanding and Treatment of Disease. New York, NY: Wiley Interscience, 2000. Pp. 227–245.
7. Aggarwal A, Kruczynski A, Frankfurter A, et al. Murine leukemia P388 vinorelbine-resistant cell lines are sensitive to vinflunine. *Invest New Drugs* 2008;26:319–330.
8. Jordan MA, Horwitz SB, Lobert S, et al. Exploring the mechanisms of action of the novel microtubule inhibitor vinflunine. *Semin Oncol* 2008;35:S6–S12.
9. Lobert S, Ingram JW, Hill BT, et al. A comparison of thermodynamic parameters for vinorelbine- and vinflunine-induced tubulin self-association by sedimentation velocity. *Mol Pharmacol* 1998;53:908–915.
10. Lobert S, Puozzo C. Pharmacokinetics, metabolites, and preclinical safety of vinflunine. *Semin Oncol* 2008;35:S28–S33.
11. Bellmunt Molins J, von der Maase H, Theodore C, et al. Randomised phase III trial of vinflunine (V) plus best supportive care (B) vs B alone as 2nd line therapy after a platinum-containing regimen in advanced transitional cell carcinoma of the urothelium (TCCU). *J Clin Oncol (Meeting Abstracts*) 2008;26:5028.
12. Kaleta R, Chung HC, Park SR, et al. Single agent IV vinflunine (VFL) in the second-line treatment of patients (pts) with advanced gastric cancer (AGC): initial results of a phase II trial. *J Clin Oncol (Meeting Abstracts)* 2008;26:15533.
13. Krzakowski M, Douillard J, Ramlau R, et al. Phase III study of vinflunine versus docetaxel in patients (pts) with advanced non-small cell lung cancer (NSCLC) previously treated with a platinum-containing regimen. *J Clin Oncol (Meeting Abstracts)* 2007;25:7511.
14. Meluch AA, Spigel DR, Burris HA III, et al. Vinflunine (VFL) as salvage chemotherapy in hormone-refractory prostate cancer (HRPC). *J Clin Oncol (Meeting Abstracts)* 2008;26:16059.
15. Saliba F, Paule B, Adam R, et al. Vinflunine in patients with advanced unresectable hepatocellular carcinoma and liver impairment. *J Clin Oncol (Meeting Abstracts)* 2007;25:15023.
16. Talbot DC, Margery J, Dabouis G, et al. Phase II study of vinflunine in malignant pleural mesothelioma. *J Clin Oncol* 2007;25:4751–4756.
17. Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *J Natl Cancer Inst* 2000;92:205–216.
18. Kaplan E, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc* 1958;53:457–481.
19. Hanna N, Bunn PA Jr, Langer C, et al. Randomized phase III trial comparing irinotecan/cisplatin with etoposide/cisplatin in patients with previously untreated extensive-stage disease small-cell lung cancer. *J Clin Oncol* 2006;24:2038–2043.
20. Joppert M, Knapp M, Dakhil SR, et al. A phase II trial of single-agent vinflunine as second-line treatment for advanced non-small cell lung cancer (An International Oncology Network Study, #I-05-009). *J Clin Oncol (Meeting Abstracts)* 2008;26:19033.